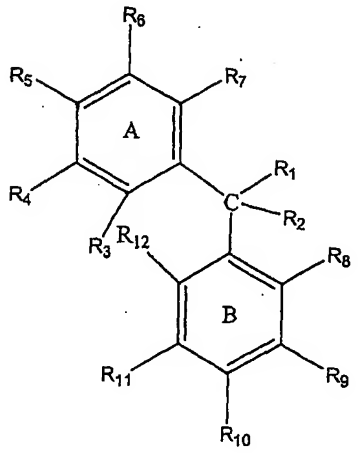
CLAIMS

1. Use of a compound having the formula I



Formula I

wherein A and B are rings linked together by a bridge C and independently represent benzene, pyridine or pyrimidine rings;

the bridge C is a carbon atom, a nitrogen, an oxygen or a sulphur atom;

R_1 and R_2 independently are H, OH, a C_{1-6} linear or branched alkoxy chain or a C_{1-20} linear or branched alkyl chain, or a C_{1-6} linear or branched alkoxy or C_{1-20} linear or branched alkyl chain having one or more of 1-2 double bonds, 1 triple bond, 1-4 oxygen functions, 1-3 nitrogen-, 1-3 halogen- or 1-2 sulphur-containing substituents, 1-2 phosphate groups, 1-2 non-substituted or substituted phenyl or cyclohexyl groups, or 1-2 five- or six-membered heterocyclic rings; or R_1 and R_7 together are said alkyl or alkoxy chain bonded directly to a carbon atom in the ring A or via a carbon, oxygen, nitrogen or sulphur atom; or R_1 and R_2 together form a double bond to the optionally substituted C_{1-20} linear or branched alkyl chain, to an oxo group, to a sulphur atom or to a nitrogen atom substituted with H, OH, an alkyl or alkoxy group; and

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12}, which can be the same or different, are selected from the group consisting of H, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OC(CH_3)_3$, $OCHCH_2$, $OCHCHCH_3$, OCH_2CHCH_2, OCCH, OCOH, $OCO(CH_2)_{0-18}CH_3$, OCH_2OH, OCHO, OCOOH, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOOCH_3$, $OCOOC_2H_5$, $OCOOC_3H_7$, OCH_2OOCH, OCH_2OOCCH_3, $OCH_2OOCC_2H_5$, OCH_2CH_2OH, OCH_2CHO, OCH_2COOH, $OC_2H_4CH_2OH$, OC_2H_4CHO, OC_2H_4COOH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CHCH_2$, $CHCHCH_3$, CH_2CHCH_2, CCH, CH_2OH, CHO, COOH, $COCH_3$, COC_2H_5, COC_3H_7, $COOCH_3$, $COOC_2H_5$,

$COOC_3H_7$, CH_2OOCH, CH_2OOCCH_3, $CH_2OOCC_2H_5$, CH_2CH_2OH, CH_2CHO, CH_2COOH, $C_2H_4CH_2OH$, C_2H_4CHO, C_2H_4COOH, F, Cl, Br, I, CF_3, CN, NH_2, NO_2, CH_2CN, CH_2NH_2,, CH_2NO_2, $CONH_2$, $CONHCH_3$, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $NHCOCH_3$, $NHNHCOCH_3$, $NHNHCONH_2$, SCH_3, OPO_3 and $OSi(CH_3)_2C(CH_3)_3$; or

wherein two of R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} on adjacent carbon atoms in the rings A and B together are $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $O(CH_2)_{1-3}O$, $OCHCH_3O$, $OC(CH_3)_2O$, $OCOO$, $OCOCH_2$, $NHCH_2CH_2$, or $NHCOCH_2$;

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

i) R_3 and R_6 must not both be H when R_7 is H or forms a bond with R_1 being a C_{1-5} linear or branched alkyl chain optionally having a double bond; or

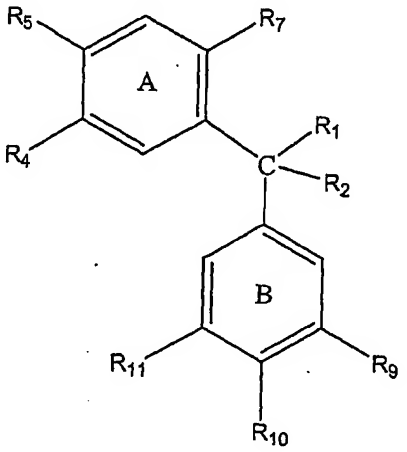
ii) R_8, R_9, R_{10}, R_{11} and R_{12} must not be 1-3 OCH_3 and 2-4 H, or 1 OCH_3 and 2 OH and 2 H, or 1 OCH_3 and 1 OH and 3 H, or 2 OCH_3 and 1 OH and 2 H; or

iii) and when R_2 is H, then R_1 must not be H, OH, OCH_3, OC_2H_5, or a C_{1-5} linear or branched alkyl chain optionally having a double bond or together with R_7 forming a bond to the carbon atom in the ring A, and with 0-3 oxygen functions; or

iv) and when R_2 is H, then the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm;

as a specific inhibitor of tyrosine phosphorylation of the insulin-like growth factor-1 receptor.

2. Use according to claim 1 of a compound having the formula Ib



Formula Ib

wherein A and B represent benzene rings and C is a carbon atom;

R_1 and R_2, which can be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2CHCH_2, $CH_2CH(CH_3)_2$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2CH_3$, OCH_2CHCH_2, $OCH_2CH(CH_3)_2$, CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, OCH_2OH, OCH_2CH_2OH, $OCH_2CH_2CH_2OH$, a phenyl, piperidinyl and morpholino group; or R_1 and R_2 together are O, CH_2, $CHCH_3$, $CHCH_2CH_3$, $C(CH_3)_2$, $CHCH(CH_3)_2$, $C(CH_2CH_3)$phenyl, NOH, $NOCH_3$, $NOCH_2CH_3$ or $NOCH_2CH_2CH_3$; and

R_4, R_5, R_7, R_9, R_{10} and R_{11}, which may be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CHCH_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, OCH_2CHCH_2, CH_2OH, CH_2CH_2OH, OCH_2OH, OCH_2CH_2OH, $COOCH_3$, F, Cl, CF_3, NH_2, $NHCH_3$, $OCO(CH_2)_{0\text{-}18}CH_3$ and OPO_3; or wherein R_4 and R_5 and/or R_9 and R_{10} together are a methylenedioxy group;

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

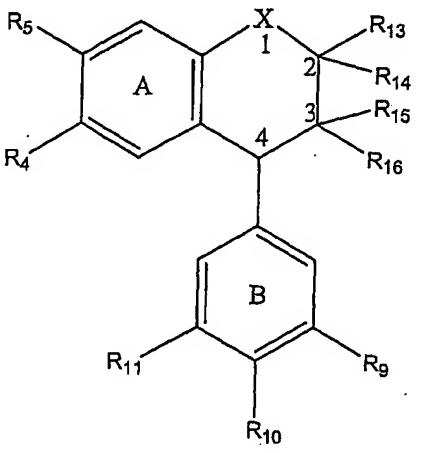
i) R_7 must not be H; or

ii) R_9, R_{10}, and R_{11} must not be 1-3 OCH_3 and 0-2 H, or 1 OCH_3 and 2 OH, or 1 OCH_3 and 1 OH and 1 H, or 2 OCH_3 and 1 OH; or

iii) and when R_2 is H, then R_1 must not be H, OH, OCH_3, OC_2H_5, or a $C_{1\text{-}5}$ linear or branched alkyl chain optionally having a double bond and/or 1-3 oxygen functions; or

iv) and when R_2 is H, then the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm.

3. Use according to claim 1 of a compound of the formula II



Formula II

wherein A and B represent benzene rings;

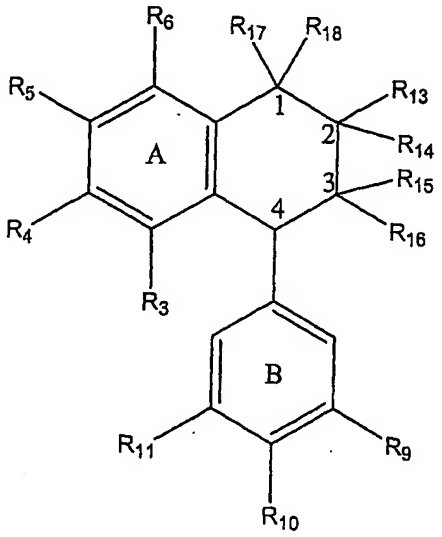
X is O, NH, NCH_3, NCH_2CH_3, NOH, $NOCH_3$, S or SO_2;

R_4, R_5, R_9, R_{10} and R_{11}, which may be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CHCH_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, OCH_2CHCH_2, CH_2OH, CH_2CH_2OH, OCH_2OH, OCH_2CH_2OH, $COOCH_3$, F, Cl, CF_3, NH_2, $NHCH_3$, $OCO(CH_2)_{0-18}CH_3$ and OPO_3; or R_4 and R_5 and/or R_9 and R_{10} together are a methylenedioxy group; and

R_{13}, R_{14}, R_{15} and R_{16}, which can be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2CHCH_2, $CH_2CH(CH_3)_2$, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2CH_3$, OCH_2CHCH_2, $OCH_2CH(CH_3)_2$, CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, OCH_2OH, OCH_2CH_2OH, $OCH_2CH_2CH_2OH$, a phenyl, piperidinyl and morpholino group; or R_{14} and R_{15} together form a double bond between the carbon atoms 2 and 3.

4. Use of a compound of the formula II according to claim 3, wherein R_{13} and R_{14} together or R_{15} and R_{16} together are O, or R_{14} and R_{15} together are selected from the group consisting of CH_2OCO, $COOCH_2$, CH_2OCH_2, CH_2CH_2CO, $CH_2OC(CH_3)_2OCH_2$, $OC(CH_3)_2O$, $CH_2OCOOCH_2$, OCOO, $CH_2OCH_2OCH_2$ and OCH_2O.

5. Use according to claim 1 of a compound of the formula III



Formula III

wherein A and B represent benzene rings;

R_3, R_4, R_5, R_6, R_9, R_{10} and R_{11}, which may be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CHCH_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, OCH_2CHCH_2, CH_2OH, CH_2CH_2OH, OCH_2OH, OCH_2CH_2OH, $COOCH_3$, F, Cl, CF_3, NH_2, $NHCH_3$, $OCO(CH_2)_{0-18}CH_3$ and OPO_3; or R_4 and R_5 and/or R_9 and R_{10} together are a methylenedioxy group;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17} and R_{18}, which can be the same or different, are selected from the group consisting of H, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2CH_3$, OCH_2CHCH_2, $OCH_2CH(CH_3)_2$, CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, OCH_2OH, OCH_2CH_2OH, $OCH_2CH_2CH_2OH$, a phenyl, piperidinyl and morpholino group; or R_{15}, R_{16}, R_{17} and R_{18} are CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2CHCH_2, or $CH_2CH(CH_3)_2$; or R_{13} and R_{14} together or R_{14} and R_{15} together or R_{17} and R_{18} together are O; or R_{14} and R_{15} together are $OC(CH_3)_2O$, OCOO or OCH_2O; or R_{14} and R_{15} form a double bond between the carbon atoms 2 and 3;

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

i) R_3 and R_6 must not both be H; or

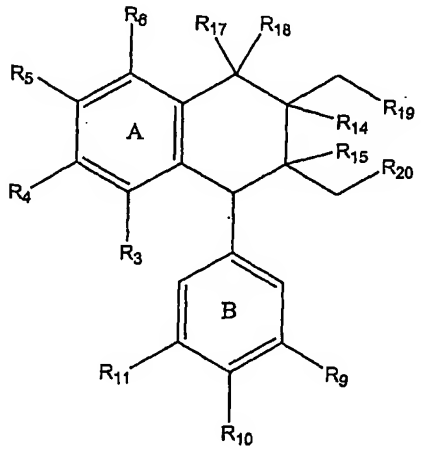
ii) R_9, R_{10} and R_{11} must not be 1-3 OCH_3 and 0-2 H, or 1 OCH_3 and 2 OH, or 1 OCH_3 and 1 OH and 1 H, or 2 OCH_3 and 1 OH; or

iii) R_{13} and R_{14} together, R_{15} and R_{16} together, or R_{17} and R_{18} together must not be O; or

iv) and when R_{13}, R_{15} and R_{17} are H, R_{14}, R_{16} and R_{18} must not be only H, OH or OCH_3 or R_{14} and R_{16} together or R_{14} and R_{18} together must not form a methylenedioxy group, acetonide group or a carbonate group; or

v) the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm.

6. Use according to claim 1 of a compound of the formula IV



Formula IV

wherein A and B represent benzene rings;

R_3, R_4, R_5, R_6, R_9, R_{10} and R_{11}, which may be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CHCH_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, OCH_2CHCH_2, CH_2OH, CH_2CH_2OH, OCH_2OH, OCH_2CH_2OH, $COOCH_3$, F, Cl, CF_3, NH_2, $NHCH_3$, $OCO(CH_2)_{0-18}CH_3$ and OPO_3; or R_4 and R_5 and/or R_9 and R_{10} together are a methylenedioxy group;

R_{14} and R_{15}, which can be the same or different, are H, OH, CH_3 or OCH_3;

R_{17} and R_{18}, which can be the same or different, are H, OH, CH_3,CH_2CH_3,OCOH, $OCO(CH_2)_{0-18}CH_3$, OCH_3, OC_2H_5 or OPO_3; or R_{17} and R_{18} together are O, CH_2, $CHCH_3$, NOH, $NOCH_3$, $NOCH_2CH_3$;

R_{19} and R_{20}, which can be the same or different, are H, OH, OCH_3, OC_2H_5, $OOCH_3$, $OOCH_2CH_3$, OCOH, or $OCO(CH_2)_{0-18}CH_3$,; or R_{19} and R_{20} together are O, CH_2, $CHCH_3$, NOH, $NOCH_3$, $NOCH_2CH_3$ or a methylene bridge, an ether or a lactone group;

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

i) R_3 and R_6 must not both be H; or

ii) R_9, R_{10} and R_{11} must not be 1-3 OCH_3 and 0-2 H, or 1 OCH_3 and 2 OH, or 1 OCH_3 and 1 OH and 1 H, or 2 OCH_3 and 1 OH; or

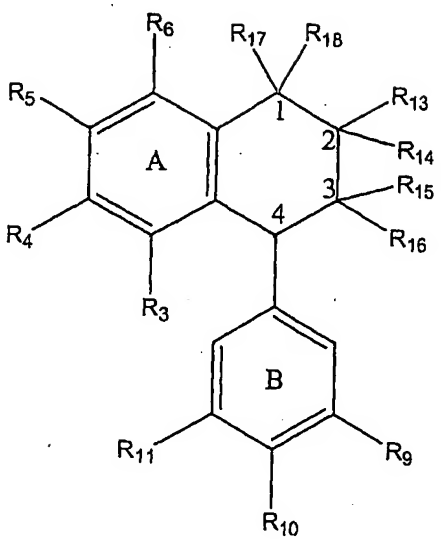
iii) and when R_{14}, R_{15} and R_{17} are H, then R_{18}, R_{19} and R_{20} must not only be H, OH, OCH_3 or OC_2H_5, or R_{19} and R_{20} must not be $OOCH_3$ or $OOCH_2CH_3$ or R_{19} and R_{20} together must not be an ether or a lactone group; or

iv) and when R_{14} and R_{15} are H, then R_{17} and R_{18} together must not be O in combination with R_{19} and R_{20} being H, OH, OCH_3 or OC_2H_5, or R_{19} and R_{20} being $OOCH_3$ or $OOCH_2CH_3$ or R_{19} and R_{20} together being an ether or a lactone group; or

v) the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm.

7. Use according to claim 6 of a compound selected from the group consisting of 4,5-demethylene-deoxypodophyllotoxin, 4,5-dimethoxy-deoxypodophyllotoxin, 4,5-dimethoxy-deoxypicropodophyllin, beta-picropeltatin, beta-picropeltatin disodium phosphate, beta-picropeltatin valerate, picropodophyllin disodium phosphate, picropodophyllin valerate, austrobailignan 1, austrobailignan 2, austrobailignan 3, polygamatin and picropolygamatin.

8. A compound of the formula III



Formula III

wherein A and B represent benzene rings;

R_3, R_4, R_5, R_6, R_9, R_{10} and R_{11}, which can be the same or different, are selected from the group consisting of H, OH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2CHCH_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, OCH_2CHCH_2, CH_2OH, CH_2CH_2OH, OCH_2OH, OCH_2CH_2OH, $COOCH_3$, F, Cl, CF_3, NH_2, $NHCH_3$, $OCO(CH_2)_{0\text{-}18}CH_3$ and OPO_3; or R_4 and R_5 and/or R_9 and R_{10} together are a methylenedioxy group;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17} and R_{18}, which can be the same or different, are selected from the group consisting of H, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2CH_3$, OCH_2CHCH_2, $OCH_2CH(CH_3)_2$, CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, OCH_2OH, OCH_2CH_2OH, $OCH_2CH_2CH_2OH$, a phenyl, piperidinyl and morpholino group; or R_{15}, R_{16}, R_{17} and R_{18} are CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, CH_2CHCH_2, or $CH_2CH(CH_3)_2$; or R_{13} and R_{14} together or R_{14} and R_{15} together or R_{17} and R_{18} together are O; or R_{14} and R_{15} together are $OC(CH_3)_2O$, OCOO or OCH_2O; or R_{14} and R_{15} form a double bond between the carbon atoms 2 and 3;

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

i) R_3 and R_6 must not both be H; or

ii) R_9, R_{10} and R_{10} must not be 1-3 OCH_3 and 0-2 H, or 1 OCH_3 and 2 OH, or 1 OCH_3 and 1 OH and 1 H, or 2 OCH_3 and 1 OH; or

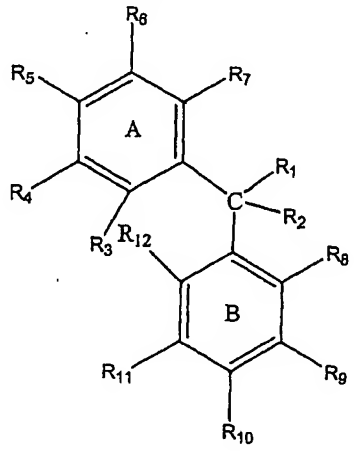
iii) R_{13} and R_{14} together, R_{15} and R_{16} together, or R_{17} and R_{18} together must not be O; or

iv) and when R_{13}, R_{15} and R_{17} are H, R_{14}, R_{16} and R_{18} must not be only H, OH or OCH_3 or R_{14} and R_{16} together or R_{14} and R_{18} together must not form a methylenedioxy group, acetonide group or a carbonate group; or

v) the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm.

9. A compound according to claim 8 for use as a medicament.

10. A pharmaceutical composition comprising a compound of the formula I



Formula I

wherein A and B are rings linked together by a bridge C and independently represent benzene, pyridine or pyrimidine rings;

the bridge C is a carbon atom, a nitrogen, an oxygen or a sulphur atom;

R_1 and R_2 independently are H, OH, a C_{1-6} linear or branched alkoxy chain or a C_{1-20} linear or branched alkyl chain, or a C_{1-6} linear or branched alkoxy or C_{1-20} linear or branched alkyl chain having one or more of 1-2 double bonds, 1 triple bond, 1-4 oxygen functions, 1-3 nitrogen-, 1-3 halogen- or 1-2 sulphur-containing substituents, 1-2 phosphate groups, 1-2 non-substituted or substituted phenyl or cyclohexyl groups, or 1-2 five- or six-membered heterocyclic rings; or R_1 and R_7 together are said alkyl or alkoxy chain bonded directly to a carbon atom in the ring A or via a carbon, oxygen, nitrogen or sulphur atom; or R_1 and R_2 together form a double bond to the optionally substituted C_{1-20} linear or branched alkyl chain, to an oxo group, to a sulphur atom or to a nitrogen atom substituted with H, OH, an alkyl or alkoxy group; and

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12}, which can be the same or different, are selected from the group consisting of H, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OC(CH_3)_3$, $OCHCH_2$,

$OCHCHCH_3$, OCH_2CHCH_2, OCCH, OCOH, $OCO(CH_2)_{0-18}CH_3$, OCH_2OH, OCHO, OCOOH, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOOCH_3$, $OCOOC_2H_5$, $OCOOC_3H_7$, OCH_2OOCH, OCH_2OOCCH_3, $OCH_2OOCC_2H_5$, OCH_2CH_2OH, OCH_2CHO, OCH_2COOH, $OC_2H_4CH_2OH$, OC_2H_4CHO, OC_2H_4COOH, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CHCH_2$, $CHCHCH_3$, CH_2CHCH_2, CCH, CH_2OH, CHO, COOH, $COCH_3$, COC_2H_5, COC_3H_7, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, CH_2OOCH, CH_2OOCCH_3, $CH_2OOCC_2H_5$, CH_2CH_2OH, CH_2CHO, CH_2COOH, $C_2H_4CH_2OH$, C_2H_4CHO, C_2H_4COOH, F, Cl, Br, I, CF_3, CN, NH_2, NO_2, CH_2CN, CH_2NH_2,, CH_2NO_2, $CONH_2$, $CONHCH_3$,

$NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $NHCOCH_3$, $NHNHCOCH_3$, $NHNHCONH_2$, SCH_3, OPO_3 and $OSi(CH_3)_2C(CH_3)_3$; or

wherein two of R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} on adjacent carbon atoms in the rings A and B together are $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $O(CH_2)_{1-3}O$, $OCHCH_3O$, $OC(CH_3)_2O$, OCOO, $OCOCH_2$, $NHCH_2CH_2$, or $NHCOCH_2$;.

with the provisos that when R_4 and R_5 together form a methylenedioxy group:

i) R_3 and R_6 must not both be H when R_7 is H or forms a bond with R_1 being a C_{1-5} linear or branched alkyl chain optionally having a double bond; or

ii) R_8, R_9, R_{10}, R_{11} and R_{12} must not be 1-3 OCH_3 and 2-4 H, or 1 OCH_3 and 2 OH and 2 H, or 1 OCH_3 and 1 OH and 3 H, or 2 OCH_3 and 1 OH and 2 H; or

iii) and when R_2 is H, then R_1 must not be H, OH, OCH_3, OC_2H_5, or a C_{1-5} linear or branched alkyl chain optionally having a double bond or together with R_7 forming a bond to the carbon atom in the ring A, and with 0-3 oxygen functions; or

iv) and when R_2 is H, then the distance between the carbon atom of the methylenedioxy group and the carbon atom of a methoxy group in the ring B must not be 0.85 – 1.05 nm;

in combination with a physiologically acceptable carrier.

11. A pharmaceutical composition according to claim 10, comprising a compound having the formula I, Ib, II, III or IV as defined in any of claims 2-8.

12. Use of a compound having the formula I, Ib, II, III or IV as defined in any of claims 1-8 for the preparation of a medicament specifically inhibiting tyrosine phosphorylation of the insulin-like growth factor-1 receptor.

13. Use of a compound having the formula I, Ib, II, III or IV as defined in any of claims 1-8 for the preparation of a medicament for prophylaxis or treatment of IGF-1R dependent diseases in vertebrates, such as benign and malignant neoplasms, the latter including carcinomas, sarcomas, neuroectodermal tumours, gliomas, myeloproliferative and lymphoproliferative diseases, and arteriosclerosis, restenosis of the coronary arteries after vascular surgery, psoriasis, certain endocrine disorders, such as acromegaly, and metabolic disorders, such as syndrome X, and also for treatment of virus infected cells and self-reactive lymphocytes (T-cells), when these cells are dependent on IGF-1R for their survival.

14. Use according to claim 13 for prophylaxis or treatment in mammals, especially humans.

15. Use of a compound having the formula I, Ib, II, III or IV as defined in any of claims 1-8 in combination with other anti-cancer treatments, including cytostatica and other anti-cancer drugs, radiation, radiotherapy and surgery, for treatment of cancer in mammals.

16. Method of treatment of a cancer in a mammal, comprising the steps of administrating a pharmaceutical composition according to claim 10 or 11 by constant infusion to a patient suffering from a tumour, monitoring the plasma level of the compound, and adjusting the rate of infusion to keep the plasma level relatively low and relatively constant for a period of time being sufficient for the tumour to be retarded or to disappear.